

## **REMARKS**

Further and favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

### **Submission of Full English Translation of Document D**

Applicants attach hereto a complete English translation of Document D ("Investigation of the Influence of AO-128 (Disaccharide-Hydrolase Inhibitor" on Sucrose Absorption"), previously submitted April 21, 2008 together with a partial English translation.

### **Claim Amendments**

Independent claims 1, 16 and 17 have been amended to recite that the hyperlipidemic agent (a) is fenofibrate or a salt thereof, and the  $\alpha$ -glucosidase inhibitor (b) comprises voglibose or a salt thereof. Additionally, the proportion of components (b)/(a) has been included in the independent claims.

In view of the above-amendments, claims 2, 3 and 6-9 have been cancelled, without prejudice or disclaimer.

No new matter has been added to the application by these amendments, since the amendments were previously present in other pending claims.

### **Patentability Arguments**

The patentability of the present invention over the disclosure of the reference relied upon by the Examiner in rejecting the claims will be apparent upon consideration of the following remarks.

### **Rejection Under 35 U.S.C. § 103(a)**

Claims 1-3, 6-17 and 19-22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Bussolari et al. (US 2003/0045553). This rejection is respectfully traversed.

(1) Difference between intestinal absorption of glucose and reabsorption of glucose in a kidney

(a) The Examiner's Position

Regarding the above absorption and reabsorption of glucose, the Examiner takes the following position:

“interpreted broadly, to inhibit reabsorption of glucose is to decrease the action or function of reabsorption of glucose. This may be achieved by limiting the amount of glucose present, thereby decreasing the action of reabsorption of glucose due to this reduced amount of glucose available to be reabsorbed”.

(b) Applicants' Arguments

(b-1) Relationship between intestinal absorption and renal reabsorption of glucose

Contrary to the Examiner's position, the renal reabsorption of glucose corresponds to a renal absorption of glucose excreted in a glomerular filtrate. Thus, such a renal reabsorption of glucose is not necessarily influenced by only taken or ingested glucose.

Glucose concentration in the blood is influenced by various factors other than taken or ingested glucose (such as glycogenolysis, glyconeogenesis, glucose availability, evacuation of sugar, etc.). In particular, high blood sugar levels are observed for diabetics, as shown in the attached Document E. (Document E: A copy of the web page “<http://www.kawasaki-dms.jp/general/rensai04/002.html>,” opened to the public by a nonprofit organization “Kawasaki Diabetes Mellitus Square”.) That is, Document E describes that sugar is always detected in the urine of a diabetic, regardless of whether preprandial or postprandial, if the blood sugar level at fasting of the diabetic is higher than 170 mg/dl. This clearly suggests that the above factors (other than taken glucose) are very influential in the glucose concentration in blood.

Most of the glucose excreted in a glomerular filtrate is absorbed in the kidney in healthy adults. Thus, a qualitative analysis of sugar in urine shows negative results for healthy adults. Therefore, it can be said that there is little or no relationship between the intake of glucose and the renal reabsorption of glucose, i.e., the renal reabsorption of glucose excreted in a glomerular filtrate is independent from taken or ingested glucose.

On the other hand, it is known that the family of glucose transporters (such as SGLT and GLUT (glucose transporter)) participate in the absorption and/or excretion of glucose. GLUT is also present in the intestines, similar to SGLT. However, voglibose does not increase blood

sugar after administration of glucose, and does not inhibit absorption of glucose, as reported by the attached Document F. (Please see page 4, left column.) (Document F: A copy of a web page “<http://www.e-search.ne.jp/~jpr/PDF/TAKEDA01.PDF>,” printed on April 21, 2009.) Document F also proves that voglibose does not act like the glucose transporters mentioned above.

It appears that the Examiner has misunderstood the relationship between the action of voglibose and glucose absorption. The following arguments are intended to clarify such a misunderstanding, as is the Figure on page 10 of this response.

Voglibose does not influence the “amount of glucose present”, since voglibose retards, rather than inhibits, the absorption of glucose. Accordingly, the position of the Examiner, as set forth in the Advisory Action, is untenable.

*(b-2) Relationship between concentration in blood and renal reabsorption of glucose*

As described above, various factors influence the serum glucose or blood sugar level. In particular, the blood sugar level of a diabetic is high, even at fasting, and excreted glucose is sometimes detected in urine. However, the phenomenon that glucose excreted in the glomerular filtrate of kidneys is reabsorbed in the kidney is called the renal reabsorption of glucose. Thus, such reabsorption of glucose is independent from intestinal absorption of glucose.

(2) Regarding the previously submitted Document D

(a) The Examiner’s Position

Regarding previously submitted Document D (“Investigation of the influence of AO-128 (disaccharide-hydrolase inhibitor) on sucrose absorption”, Clinical Diseases of Adult People, Vol.22, No.3, 1992, pages 127-134), the Examiner takes the following position:

“this evidence also teaches administration of alpha-glucosidase inhibitors ‘resulted in a small, but clinically meaningful reduction in glycosylated hemoglobin levels’, providing guidance for the medical result of a small but significant reduction in the amount of glucose present, and accordingly a reduction of actions associated with the intestinal absorption and renal reabsorption of glucose due to this reduction in the amount of glucose present.”

(b) Applicants’ Arguments

*(b-1)* The reduction of the glycosylated hemoglobin levels is caused by retarding the

conversion of foods or nutrition (e.g., sugars and carbohydrates) into glucose, and inhibiting postprandial hyperglycemia as a result of an  $\alpha$ -glucosidase inhibition by voglibose. Namely, such a reduction shows that glycosylated hemoglobin levels are reduced by suppressing the postprandial glucose concentration so as not be too high, regardless of the total amount of the absorbed glucose.

High hyperglycemia develops for a diabetic after a meal, thereby damaging the endothelial cells of blood vessels. Moreover, such damage causes arteriosclerosis or hypertension. The ability for insulin secretion or glucose availability has been deteriorated, and can be improved again by moderating changes in the concentration of glucose in the blood without drastic changes, not by inhibiting absorption of glucose. Because of such mechanisms, a diabetic complication can be effectively prevented or treated.

Postprandial hyperglycemia or hyperinsulinemia is a risk for a diabetic or a patient having an impaired glucose tolerance (IGT) to develop severe diabetes, arterioscleroses, cardiovascular diseases or the like. Such a risk is understood as being independent from a severity degree of diabetes, determined by serum glucose at fasting. Voglibose prevents a development of, or treats, the above diseases by suppressing the postprandial hyperglycemia or hyperinsulinemia. Thus, voglibose is quite different from SGLT inhibitors, in both its action and its mechanism.

Glucose in the blood is normally incorporated into cells, such as muscles, thereby slightly increasing the serum glucose level. However, the serum glucose in diabetics or patients having IGT is drastically (not slightly) increased due to an insufficient insulin secretion or other reasons. Thus, the glucose level in the blood can be sufficiently suppressed by the retardation of glucose absorption, when the glucose level in blood is the same as or less than an insulin-secreting ability of the patient. The glucose concentration and glycosylated hemoglobin level in blood is not determined based on only one factor, namely, the total absorption amount of glucose (i.e., the amount of glucose present mentioned by the Examiner).

(b-2) Further, contrary to the Examiner's position, previously submitted Document D does not provide any guidance for the reduction in the amount of glucose present in relation to the reduction in glycosylated hemoglobin levels.

The Examiner points out that voglibose results in one example for absorption inhibition of the disaccharide sucrose as only about 5%, whereas the blood sugar level decreases with

inhibition of sucrose absorption. However, the average reduction “5%” should not be noted. It would be notable that the maximum blood sugar levels “130 mg/dL” and “118 mg/dL” of the patients No.11 and No.1 are evidently reduced to “97 mg/dL” and “92 mg/dL” (i.e., the reduction levels are 33 mg/dL and 26 mg/dL), respectively, whereas reduction in the total amounts of sucrose absorption of the patients No.11 and No.1 is 0g (No.11) and 0.1g (No.1) relative to administration amount 100g of sucrose. It could never be said that the above reduction levels of 33 and 26 mg/dL are inferior to the average reduction level 26.6 mg/dL (i.e., reduction from 136.8 mg/dL to 110.2 mg/dL). (Please see Table 3 of Document D).

(b-3) Applicants respectfully assert that the Examiner has misunderstood the disclosure of previously submitted Document D.

Specifically, regarding the item “Amount of unabsorbed sucrose (g)” in Table 3, the Examiner may have understood the action of voglibose so as to be an action of inhibiting “absorption of glucose” via a glucose transporter. If this is the case, please consider the following explanations, which are provided to clarify any such misunderstanding.

Firstly, voglibose is a drug influencing the amount of glucose produced by hydrolysis of sucrose and the production rate of glucose. Moreover, voglibose reduces the production amount of glucose in vitro. However, voglibose only retards the production rate of glucose (i.e., hydrolysis rate of sucrose), and almost all of the sucrose is decomposed rather than evacuated in vivo. Thus, voglibose does not change the total absorption amount of glucose in vivo.

Details are shown in the following scheme.

Scheme 1: Action of voglibose in relation to a postprandial blood sugar level for a diabetic  
 (Action of voglibose relative to glucose absorption from a meal, and hydrolysis of sucrose to glucose).

**Behavior of glucose and sucrose:**

A diabetic (after a meal)

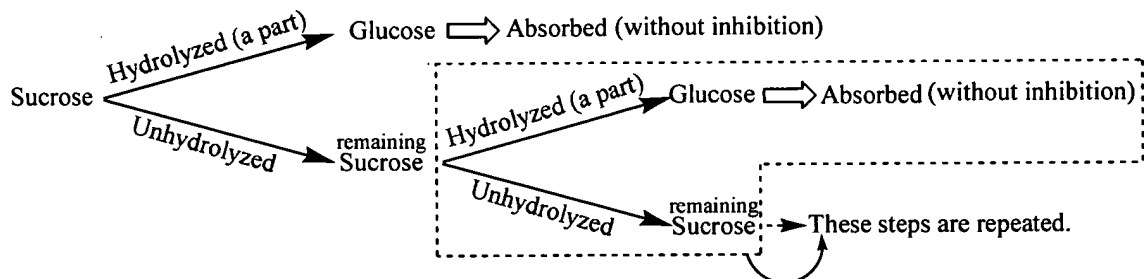
Glucose  $\Rightarrow$  Absorbed

Sucrose  $\xrightarrow{\text{Hydrolyzed}}$  Glucose  $\Rightarrow$  Absorbed

Postprandial hyperglycemia caused by deterioration of insulin-secreting ability and glucose availability.

A voglibose-administrated diabetic (after a meal)

Glucose  $\Rightarrow$  Absorbed (without inhibition)



As shown above, voglibose causes the hydrolysis of sucrose to *gradually* proceed to produce glucose. However, voglibose *does not inhibit absorption of glucose* thus produced, *nor does it inhibit glucose derived from a meal*.

Incidentally, the amount of the remaining sucrose corresponds to about 5 wt% of the amount of meal or food intake, in average. Thus, it can be said that almost all sucrose is decomposed in vivo, and there is scarcely any difference in the total amount of the produced glucose between the voglibose-administered patient and the non-voglibose administered patient.

As described above, the action and mechanism of voglibose is the retardation of sucrose hydrolysis. As a result, the absorption rate of glucose is also retarded, insulin-secreting ability

and insulin-availability of patients themselves become utilizable, thereby reducing glycosylated hemoglobin levels. In other words, glycosylated hemoglobin levels are reduced even if the total amount of glucose absorption is not reduced.

Thus, the actions and mechanisms of the drug “voglibose” are to increase the glucose concentration in blood moderately (not drastically), in order to suppress hyperglycemia, which is a risk factor of cardiovascular diseases, and to possibly keep insulin-secreting ability. These actions and mechanisms of voglibose are clearly distinct from the actions and mechanisms of a drug which inhibits the absorption of glucose.

(3) Differences in effects between voglibose or fenofibrate and a combination of both components

(a) The Examiner's Position

The Examiner takes the position that Applicants' previous comparison, in which the effects of voglibose and fenofibrate in combination is notably different from the effects of voglibose alone or the effect of fenofibrate alone, was provided to show that the provided data and therefore the scope of the claims encompassed a range wherein the effects of voglibose and the effect of fenofibrate is roughly additive.

(b) Applicants' Arguments

Contrary to the Examiner's position, the effects of the combination of voglibose and fenofibrate compared with each of these components are not additive effects, but rather are nearly synergistic.

Specifically, as apparent from Table 1 in the specification, the effects of voglibose or fenofibrate alone are estimated, based on the rate of change (%), as follows:

Effects of voglibose:

$$119.8(\%) - 104.7(\%) = 15.1(\%)$$

Effects of fenofibrate:

$$119.8(\%) - 112.2(\%) = 7.6(\%)$$

Thus, if the effects of the combination use of both components are additive, the effects have to be estimated as the sum of the above effects of each component. That is, for an additive effect, the effects would be estimated as follows:

Additive effects:

$$\underline{15.1(\%) + 7.6(\%) = 22.7(\%)}$$

However, the effects of the combination of voglibose and fenofibrate are actually provided as follows:

Effects by the combination of voglibose and fenofibrate:

$$\underline{119.8(\%) - 88.6(\%) = 31.2(\%)}$$

Thus, the actual effects achieved from the combination of fenofibrate and voglibose are clearly not additive, as asserted by the Examiner. In fact, the actually obtained rate of change (31.2%) is 37% larger than the estimated “additive” rate of change, as determined based on the following equation:

$$\underline{(31.2(\%) / 22.7(\%) - 1) \times 100 = 37 (\%)}$$

Additionally, the difference between the actual obtained rate and the estimated rate is 8.5%, as determined from the following equation:

$$\underline{31.2(\%) - 22.7(\%) = 8.5 (\%)}$$

The difference of “8.5%” is a clinically meaningful value, since this value is larger than the effect of fenofibrate alone (7.6%). Accordingly, the effect achieved from the combination of voglibose and fenofibrate is synergistic, rather than additive.

In addition to the above-comments, the Examiner is respectfully requested to reconsider the arguments set forth in the Amendment After Final Rejection, filed January 2, 2009. In view of the entirety of Applicants’ arguments, it is clear that the Examiner’s basis for maintaining the above-rejection is untenable.

Thus, for the above reasons, as well as those set forth in the Amendment filed January 2, 2009, the subject matter of Applicants’ pending claims is clearly patentable over the Bussolari et al. reference. Accordingly, it is respectfully requested that the above-rejection be withdrawn.



Conclusion

Therefore, in view of the foregoing amendments and remarks, it is submitted that the ground of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this Amendment, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

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Investigation of the Influence of AO-128  
(Disaccharide-Hydrolase Inhibitor) on Sucrose Absorption

INTRODUCTION

5           AO-128 is a disaccharide-hydrolase ( $\alpha$ -glucosidase) inhibitor which was developed by Takeda Pharmaceuticals Co., Ltd. (Fig. 1).

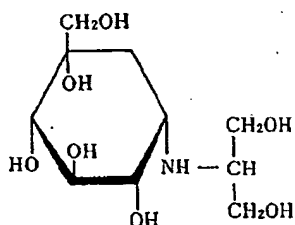


Fig. 1 Structural formula of AO-128

10           This drug is orally administered and inhibits an enzyme that decomposes disaccharide to monosaccharide, referred to as membrane digestion, in the final stage of carbohydrates digestion, thereby suppressing generation of glucose derived from carbohydrates in the food to inhibit postprandial drastic elevation of blood glucose level<sup>1)</sup>.  
15           Herefrom the application of this drug to diabetes, which is a disease of carbohydrate metabolism, is expected. We performed a phase II trial of this drug for patients with diabetes<sup>2)</sup> and found that the apparent inhibition of elevation of blood glucose level was observed.

20           On the other hand, it is reported that indigestible carbohydrates which reach intestinum crassum without being absorbed is decomposed by intestinal bacterial flora to

generate hydrogen gas, and about 10% of the generated hydrogen gas is discharged into the expired air<sup>3,4)</sup>.

Lactulose (1-4- $\beta$ -galactosido-fructose) is an artificial disaccharide. It has been acknowledged that  
5 lactulose is not decomposed by a disaccharide-hydrolase present in human being intestine and hardly absorbed<sup>5)</sup>. When lactulose is administered to human beings, hydrogen gas is discharged into the expired air<sup>6,7)</sup>. In contrast, sucrose (1-2- $\alpha$ -glucosido-fructose) is a disaccharide,  
10 which is decomposed by a disaccharide-hydrolase present in human being intestine and almost completely absorbed<sup>6,7)</sup>.

From these facts, the following approach has been examined: as the basis for the case that lactulose is  
15 administered, the amount of carbohydrates unabsorbed when a disaccharide-hydrolase inhibitor is administered in concurrence with sucrose intake is estimated based on the volume of hydrogen gas discharged into the expired air<sup>6,7)</sup>.

Now we performed this study in order to clarify a  
20 suppression mechanism of elevation of blood glucose level due to AO-128 by estimating the amount of carbohydrates unabsorbed in the administration of this drug according to Caspary's method<sup>6)</sup>.

Incidentally, this study was conducted from June  
25 through December, 1990.

## I. Test Procedure

### 1. Subjects

Among Japanese adult male volunteers, 12 persons satisfying all of the following criteria were selected as  
5 subjects.

(1) A person aged 20-59 years in principle.

(2) A person without a history of drug allergy.

(3) A person without a history of alimentary disease.

(4) A person in whom discharge of hydrogen gas into  
10 the expired air after lactulose loading (oral intake of 200 ml of water containing 13 g of lactulose) was confirmed.

(5) A person who underwent prior medical examinations such as history taking, physical examination, electrocardiogram, ordinary blood test, blood chemical test,  
15 glycohemoglobin, and urine analysis (for details of the items for examinations refer to Table 1) and was permitted as a suitable subject by the investigator.

(6) A person who agreed to the test in writing only after the person has received a full explanation of the  
20 purpose and content of the test, the effects and safety of the test drug, and others.

Table 1 Items for Examinations and Observations

Physical examination	ocular inspection, auscultation, palpation, percussion, blood pressure, pulse rate
Electrocardiogram	Resting 12-lead
Ordinary blood test	erythrocyte count, hemoglobin count, hematocrit value, platelet count, leukocyte count
Blood chemical test	blood glucose, total protein, albumin, A/G, GOT, GPT, $\gamma$ -GTP, Al-P, LDH, total bilirubin, amylase, creatinine, BUN, Na, K, Cl, Ca, P
Glycohemoglobin	hemoglobin A <sub>1c</sub>
Urine analysis	sugar, protein, urobilinogen, ketone body, deposit

Table 2 Dose, Medication and Dosing period

Prior medical examinations	Administration group	4 to 1 Day before (for 4 days)	Day 1	Days 4 to 7 (for 4 days)	Day 8
Lactulose loading <sup>1)</sup>	AP group	<ul style="list-style-type: none"> <li>● just before breakfast</li> <li>● just before lunch</li> <li>● just before supper</li> </ul>	<ul style="list-style-type: none"> <li>● under abstinence from breakfast (10 minutes before sucrose loading<sup>2)</sup>)</li> </ul>		<ul style="list-style-type: none"> <li>○ under abstinence from breakfast (10 minutes before sucrose loading<sup>2)</sup>)</li> </ul>
	PA group		<ul style="list-style-type: none"> <li>○ under abstinence from breakfast (10 minutes before sucrose loading<sup>2)</sup>)</li> </ul>	<ul style="list-style-type: none"> <li>● just before breakfast</li> <li>● just before lunch</li> <li>● just before supper</li> </ul>	<ul style="list-style-type: none"> <li>● under abstinence from breakfast (10 minutes before sucrose loading<sup>2)</sup>)</li> </ul>

1) Lactulose loading: oral intake of 200 ml of water containing 13 g of lactulose

2) Sucrose loading: oral intake of 200 ml of water containing 100 g of sucrose

● AO-123, 0.2 mg administration

○ Placebo administration

## 2. Test drug

Tablets, each containing 0.2 mg of AO-128, and placebo tablets were used. The two tablets could not be distinguished from each other.

5           Incidentally, the test drug was supplied by Takeda Pharmaceuticals Co., Ltd.

## 3. Test design

The single blind, placebo-controlled crossover test for subject was carried out.

## 10           4. Dose, medication, and dosing period

The dose, the medication, and the dosing period are shown in Table 2. For both a group administered this drug first (AP group) and a group administered placebo first (PA group), sucrose loading (oral intake of 200 ml of water  
15   containing 100 g of sucrose) was conducted twice at intervals of 7 days.

In each group, one tablet of this drug was administered three times a day just before every meal over 4 days, and one tablet was further administered with 50 ml of water  
20   10 minutes before the sucrose loading performed on the next day. The placebo was administered as single dose with 50 ml of water 10 minutes before the sucrose loading.

Incidentally, the sucrose loading was performed when a subject was hungry after the subject was fasted for not  
25   shorter than 10 hours from the night before.

## 5. Number of subjects and distribution of subjects

For the number of subjects, total 12 persons were

divided into two groups: AP group (6 persons) and PA group (6 persons). The distribution of the subjects to the AP group or the PA group was conducted randomly.

#### 6. Method for examinations and observations

5       The main items for examinations and observations and period thereof were shown in Fig. 2.

##### (1) Background

In prior medical examinations, subject name (initials), age, body height, and body weight were examined.

##### 10       (2) Medical checkup

In prior medical examinations, history taking and physical examination, electrocardiogram, and examination and measurement of glycohemoglobin were conducted (for details of the items refer to Table 1).

##### 15       (3) Lactulose loading

In the prior medical examinations, 200 ml of water containing 13 g of lactulose was taken orally.

##### (4) Sucrose loading

On each of Day 1 and Day 8, 200 ml of water containing  
20   100 g of sucrose was taken orally.

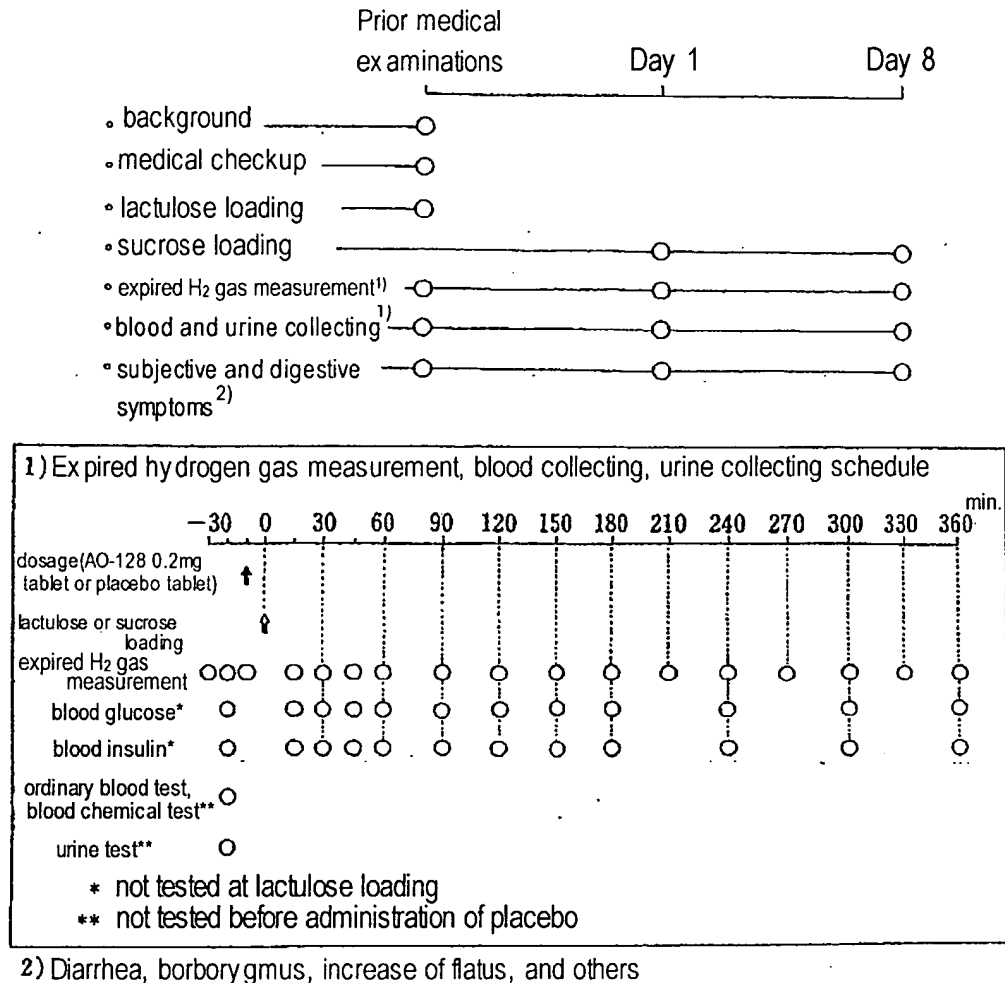


Fig. 2 Main items for examinations and observations, and period thereof

### (5) Expired hydrogen gas measurement

In each case of lactulose loading and sucrose loading, the expired hydrogen gas was measured three times at intervals of 10 minutes from 30 minutes before the loading. After the loading, the expired hydrogen gas was measured at intervals of 15 minutes up to 60 minutes after the loading, thereafter at intervals of 30 minutes up to 360 minutes after the loading.

The measurement was performed by using a Microlyzer



Model 12i (registered trademark) (manufactured by QPINTRON)  
gas chromatography.

(6) Blood glucose and blood insulin

The measurements of blood glucose and blood insulin  
5 were conducted at intervals of 15 minutes before the sucrose  
loading and up to 60 minutes after the loading, thereafter  
at intervals of 30 minutes up to 180 minutes after the loading,  
and further thereafter at intervals of 60 minutes up to  
360 minutes after the loading. The total number of  
10 measurements was 12.

The blood glucose was measured by using plasma  
according to an electrode method, and the blood insulin  
was measured by using serum according to RIA.

(7) Clinical examination

15 In the prior medical examination and before the final  
administration of this drug, the examinations and  
measurements of the items shown in Table 1 were performed  
for an ordinary blood test, a blood chemical test, and a  
urine analysis.

20 Each of the examination data was judged whether the  
obtained value was normal or abnormal. The presence of any  
abnormal fluctuation (ingravescence) was evaluated in  
comparison with the prior medical examination when the  
administration of this drug had been completed. When any  
25 abnormal fluctuation was "present", the follow-up research  
was conducted, and the relationship between the abnormal  
fluctuation and this drug was judged on the basis of the

following 5 types: "apparently relevant", "probably relevant", "slightly relevant", "unclearly relevant (reservation of judgment)", and "not relevant".

(8) Subjective symptom and digestive symptom

5            Subjective symptoms for the duration of the test, particularly a digestive symptom (diarrhea, loose stool, bellyache, bloating sensation, borborygmus, and increase of flatus) after lactulose or sucrose loading, were investigated. If any symptoms appears, the relationship  
10 between this drug and the degree (mild, moderate, severe), the onset time, and the treatment and outcome (disappearance, remission, constancy, deterioration) of the symptoms was judged on the basis of the same five types as the case of the clinical examination.

15            7. Comparison and discussion items

(1) Area under concentration-time curve of expired hydrogen gas

The concentration of the expired hydrogen gas was measured three times every subject before every lactulose  
20 or sucrose loading, and the average value of the three times was given as a control for every subject. The variation changed from the control was regarded as a value at each measuring points.

The area under the concentration-time curve of the  
25 expired hydrogen gas after the sucrose loading following the administration of this drug was determined by subtracting the area measured after the sucrose loading

following the administration of the placebo, where it was assumed that all of the loaded sucrose was absorbed, from the found value. That is, for every measuring point in each subject, the difference between the value after the administration of this drug (hereinafter "A") and the value after the administration of the placebo (hereinafter "P"), "A-P", was determined, and the area under the concentration-time curve of the expired hydrogen gas after the sucrose loading following the administration of this drug was calculated by using the value "A-P" according to a trapezoidal method [hereinafter "AUC(A-P)"].

In the same manner, the area under the concentration-time curve of the expired hydrogen gas after the lactulose loading was calculated by using the difference between the value after the lactulose loading (hereinafter "L") and the value "P" ("L-P") [hereinafter "AUC(L-P)"].

The amount of the unabsorbed sucrose due to the administration of this drug (the amount of sucrose which was not absorbed) was calculated based on the following equation.

Amount of the unabsorbed sucrose (g) =

Amount of lactulose (g) x AUC(A-P)/(AUC(L-P))

Table 3 Case List

Subject No.	Initials	Age (year)	Body height (cm)	Body weight (kg)	Amount of unabsorbed sucrose (g)	Maximum blood glucose (mg/dl)		Digestive symptoms		
						P	A	L	P	A
1	K.H.	18	172	51	0.1	118	92	Borborygmus	-	-
2	K.M.	20	165	76	8.2	143	131	-	-	-
3	S.H.	25	166	73	9.0	172	153	-	-	-
4	Y.Y.	20	169	63	6.1	128	114	-	-	-
5	M.H.	22	175	74	1.8	134	112	-	-	Diarrhea
6	S.I.	20	178	67	3.6	133	120	-	-	-
7	Y.I.	20	172	63	5.5	147	99	Bellyache	-	Loose stool
8	R.A.	20	171	65	7.2	154	116	-	-	Loose stool
9	K.W.	20	173	60	8.3	111	87	-	-	Bloating sensation
10	S.O.	20	163	57	7.7	126	95	-	-	-
11	M.M.	21	170	75	0	130	97	-	-	-
12	K.I.	20	171	55	2.2	145	106	-	-	-
Average		20.5	170.4	64.9	5.0	136.8	110.2			
± standard deviation		±1.7	±4.2	±8.3	±3.3	±16.6	±18.7			

(Note) P: After 100 g of sucrose loading following administration of placebo

A: After 100 g of sucrose loading following administration of 0.2 mg of AO-128

L: After 13 g of lactulose loading

-: No symptoms

(2) Blood glucose and blood insulin after sucrose loading

The blood glucose and area under concentration-time curve of the blood glucose as well as the blood insulin and area under concentration-time curve of the blood insulin after the administration of this drug were compared with those after the administration of the placebo to examine the change of the response of the blood glucose and blood insulin to 100 g of sucrose loading due to the administration of this drug.

The area under concentration-time curve of the blood glucose and the area under concentration-time curve of the blood insulin were calculated by using the increase levels from the blood glucose and blood insulin values before the sucrose loading until the time at which the blood glucose and blood insulin values after the sucrose loading were recovered to those values before the sucrose loading, respectively, according to the trapezoidal method (hereinafter an area under concentration-time curve of the elevation of blood glucose level and an area under concentration-time curve of the elevation of blood insulin level).

## II. Test results

The background of the twelve subjects are shown in Table 3; the average age was  $20.5 \pm 1.7$  (average value  $\pm$  standard deviation), the average body height was  $170.4 \pm$

4.2 cm (same as above), and the average body weight was  $64.9 \pm 8.3$  kg (same as above).

Hereinafter, the calculated value was indicated as the average value  $\pm$  standard deviation of 12 subjects.

5            1. Area under concentration-time curve of expired hydrogen gas

The changes of the concentration of the expired hydrogen gas are shown in Fig. 3. The value before the lactulose loading on the day of the lactulose loading was  
10  $17.8 \pm 8.5$  ppm, and the values before the sucrose loading on the day of the sucrose loading were  $24.8 \pm 15.9$  ppm before the administration of this drug and  $21.8 \pm 17.4$  ppm before the administration of the placebo. There was little difference among these values.

15            The concentration-time curve of the expired hydrogen gas was shown in terms of average value in the order of lowest to highest as follows: after 13 g of lactulose loading, after 100 g of sucrose loading following the administration of this drug, and after 100 g of sucrose loading following  
20 the administration of the placebo. The discharge of hydrogen gas after the administration of this drug was lower than that after the lactulose loading.

Regarding the area under concentration-time curve of the expired hydrogen gas until 360 minutes (6 hours)  
25 after the loading, the area after the sucrose tolerance under the administration of this drug [AUC(A-P)] was  $98.4 \pm 69.9$   $\Delta$ ppm·hr, and the area after the lactulose tolerance

[AUC(L-P)] was  $259.0 \pm 130.1 \Delta\text{ppm}\cdot\text{hr}$ . The amount of the unabsorbed sucrose calculated every subject, that is, the amount of sucrose which this drug inhibited from being absorbed, is shown in Table 3, and the average value thereof was  $5.0 \pm 3.3 \text{ g}$ .

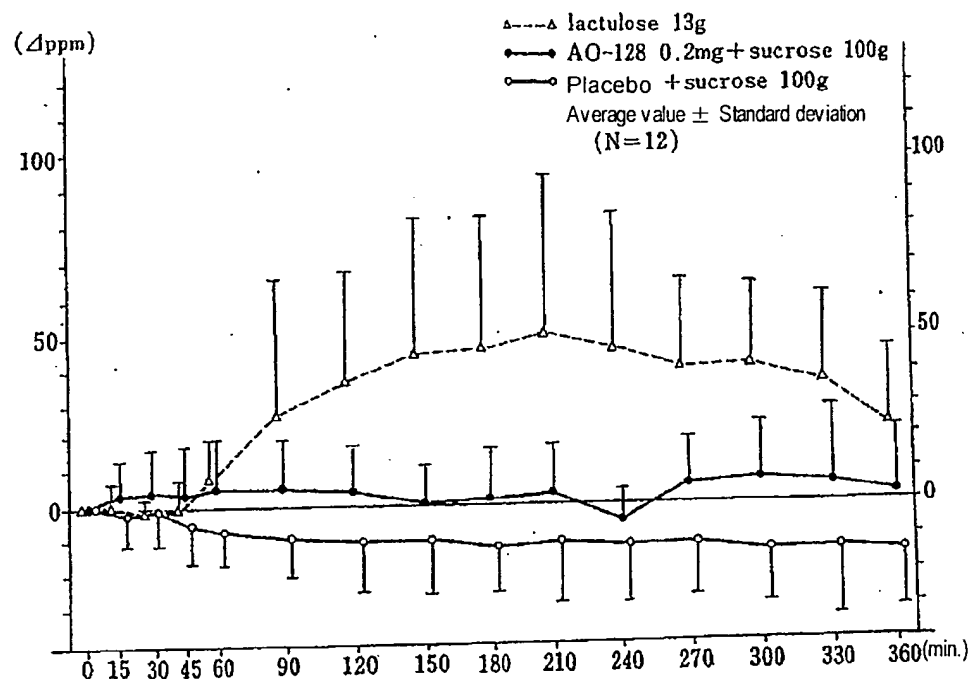


Fig. 3 Changes in concentration of expired hydrogen gas

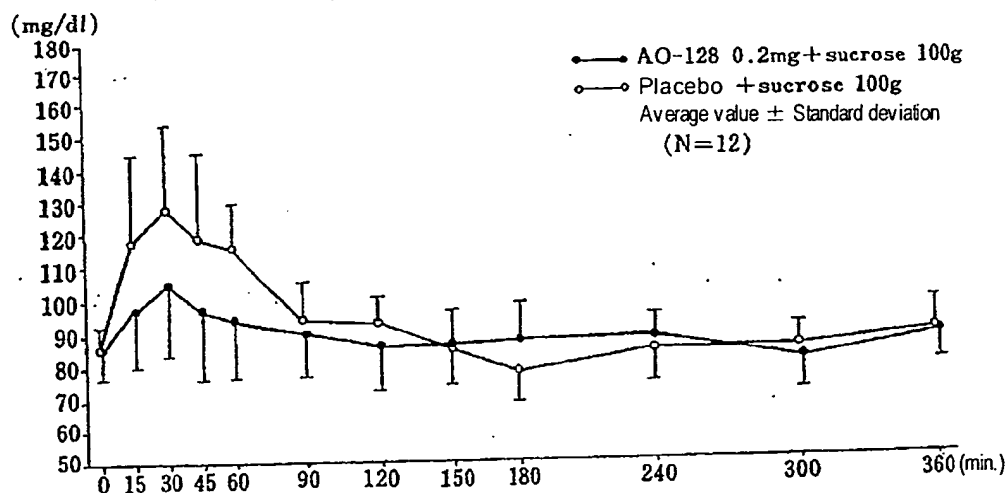


Fig. 4 Changes of blood glucose

## 2. Blood glucose and blood insulin

### (1) Blood glucose

The changes in the average of the blood glucose level after the administration of this drug and that after the administration of the placebo are shown in Fig. 4. The values before sucrose loading were the same values,  $86 \pm 7$  mg/dl, in both before the administration of this drug and before the administration of the placebo.

After the administration of the placebo, the blood glucose level reached the maximum value ( $128 \pm 26$  mg/dl) 30 minutes after the sucrose loading and the minimum value ( $77 \pm 9$  mg/dl) 180 minutes after the sucrose loading. The minimum value was further lower than the value before the sucrose loading.

After the administration of this drug, the blood glucose level reached the maximum value 30 minutes after the sucrose loading as with the administration of the placebo, while the maximum value ( $105 \pm 21$  mg/dl) was apparently lower than that after the administration of the placebo. Moreover, concerning 15 minutes, 45 minutes, and 60 minutes after of the sucrose loading, the values after the administration of this drug were apparently lower than those after the administration of the placebo. However, concerning 180 minutes after the sucrose loading, the value after the administration of this drug ( $86 \pm 11$  mg/dl) was higher than that after the administration of the placebo. On the other hand, the minimum value was  $79 \pm 7$  mg/dl 300



minutes after the sucrose loading.

Moreover, with respect to the maximum blood glucose value after the sucrose loading every subject, all subjects showed lower values after the administration of this drug compared with the value after the administration of the placebo, as shown in Table 3.

The average value of the area under concentration-time curve of the elevation of blood glucose level after the administration of this drug was  $20.4 \pm 20.0 \Delta\text{mg}\cdot\text{hr}/\text{dl}$ , which was reduced to about 40% of that after the administration of the placebo,  $47.2 \pm 24.3 \Delta\text{mg}\cdot\text{hr}/\text{dl}$ .

## (2) Blood insulin

The changes of the average of the blood insulin after the administration of this drug or that after the administration of the placebo are shown in Fig. 5.

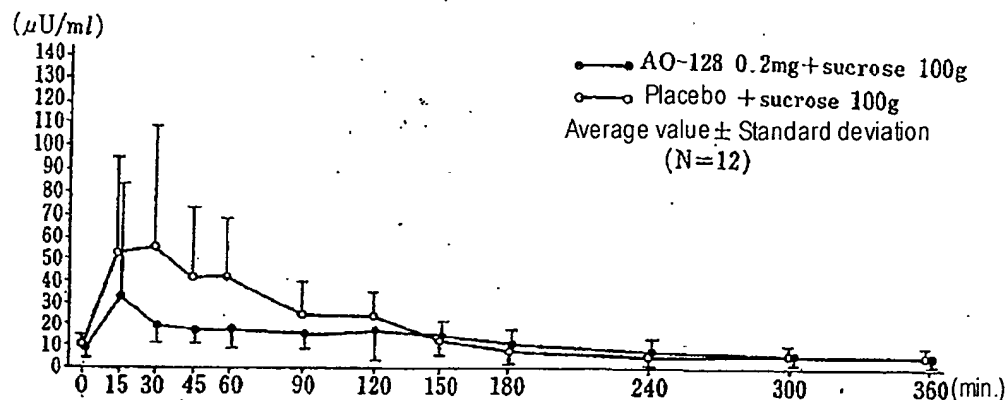


Fig. 5 Changes of blood insulin

With respect to the value before the sucrose loading, the value before the administration of this drug was  $7 \pm 2 \mu\text{U}/\text{ml}$ , which was slightly lower than that before the

administration of the placebo,  $10 \pm 5 \mu\text{U/ml}$ .

The change of the blood insulin after 100 g of sucrose loading almost corresponds to the change of the blood glucose, in both cases after the administration of this drug and  
5 after the administration of the placebo.

However, the blood glucose after the administration of this drug reached the maximum value 30 minutes after the sucrose loading, while the blood insulin reached the maximum value 15 minutes after the sucrose loading.

10 In the same manner as in the blood glucose, the area under concentration-time curve of the elevation of blood insulin level after the administration of this drug was  $37.5 \pm 27.8 \Delta\mu\text{U}\cdot\text{hr/dl}$ , which was reduced to about 60% of that after the administration of the placebo,  $62.4 \pm 34.3$   
15  $\Delta\mu\text{U}\cdot\text{hr/dl}$ .

### 3. Clinical examination

In all subjects, any abnormal changes of the clinical examination values which could not deny any relationship to this drug were not observed.

### 20 4. Digestive symptom

As shown in Table 3, among 12 subjects, one subject with borborygmus and one subject having bellyache (total: 2 subjects) were found after 13 g of lactulose loading. No one developed any symptoms after the administration of  
25 the placebo.

Moreover, 4 subjects out of 12 subjects developed any symptoms after the administration of this drug. The

details were two subjects with loose stool, one subject with diarrhea and one subject with bloating sensation. All of these symptoms rapidly disappeared after the completion of the administration.

5

### III. Discussion

Generally, when malabsorption of carbohydrates occurs due to alactasia or other causes, carbohydrates which reached intestinum crassum without being absorbed are  
10 regarded as decomposing by intestinal bacterial flora to generate a gas such as hydrogen, carbon dioxide, methane and an organic acid such as acetic acid or butyric acid<sup>8)</sup>. It is reported that, among them, about 10% of the hydrogen gas generated is discharged into the expired air<sup>3,4)</sup>.

15 By applying this principle, some approaches for estimating the amount of the unabsorbed carbohydrates have been conducted, as the basis for the volume of hydrogen gas discharged into the expired air when a carbohydrate (lactulose) unabsorbed in the human being is  
20 administered<sup>6,7)</sup>.

AO-128 is a disaccharide-hydrolase inhibitor and orally administered to suppress a drastic increase of blood glucose after a meal by inhibiting  $\alpha$ -glucosidase existing in the small intestine and suppressing generation of glucose  
25 derived from carbohydrates in the food<sup>1)</sup>. If the action mechanism of this drug for inhibiting the elevation of blood glucose level arises from inhibition of absorption,

unabsorbed carbohydrates reach intestinum crassum directly to generate hydrogen gas.

Based on the mentioned above, the amount of sucrose unabsorbed in spite of administering this drug was estimated according to the ratio of the volume of hydrogen gas discharged into the expired air after taking sucrose following the administration of this drug relative to the volume of hydrogen gas discharged into the expired air after the administration of lactulose. This study was performed in this manner in order to determine the action mechanism of this drug for inhibiting the elevation of blood glucose level arising from inhibition of absorption.

Incidentally, prior to the implementation of this study, a preliminary study was conducted in order to set the dose regimen and dose of this drug as well as the amounts of lactulose and sucrose loading. Tablets and solutions containing this drug were used and examined for single dose and repeated dose. For a dose, 0.2 mg, 0.4 mg, 0.5 mg, and 1.0 mg of this drug were used. As a result, when not less than 0.5 mg of this drug was administered for a dose, digestive symptom occurred in a high frequency. When 0.4 mg of this drug was administered for a dose, digestive symptom was not observed, while there was suspicion that digestive symptom occurred in some cases. On the other hand, when 0.2 mg of this drug was administered for a dose, hydrogen gas discharged into the expired air was hardly observed in single dose and was observed in repeated dose.

Accordingly, the dose regimen and dose of this drug were determined as a repeated dose and 0.2 mg for a dose. Since the approximately same level of hydrogen gas discharge was observed in the administration of the tablet and that of the solution, and the tablet was chosen. Moreover, 6.5 g, 10 g and 13 g of lactulose loading and 75 g and 100 g of sucrose loading were performed and revealed, that each was drinkable. Accordingly, the amounts of lactulose and sucrose were determined as 13 g and 100 g, respectively.

As a result, the amount of the unabsorbed sucrose which was estimated based on the ratio  $AUC(A-P)/AUC(L-P)$  in the area under concentration-time curve of the expired hydrogen gas, that is, the amount of the sucrose which this drug inhibited from being absorbed, was merely about 5.0 g, whereas the loaded amount was 100 g. Accordingly, the inhibition amount of the sucrose absorption due to the administration of 0.2 mg of this drug for a dose was extremely low, and the sucrose was mostly absorbed.

As shown in Fig. 4, both of sharp elevation and degradation of the blood glucose due to the sucrose loading following the administration of the placebo were apparently inhibited after the administration of this drug, and the blood glucose curve underwent a gradual change. Moreover, the maximum blood glucose value or area under concentration-time curve of the blood glucose after the administration of this drug apparently decreased or reduced compared with that after the administration of the placebo.

That is, suppression in increase of blood glucose was evidently recognized by administration of this drug, even though the amounts of the sucrose absorptions do not make much difference between the administration of the placebo  
5 and the administration of this drug. Thus, regarding the action mechanism of the suppression in blood glucose-increase by this drug in a dose of 0.2 mg, the absorption of a carbohydrate is inhibited but the degree of the inhibition is quite low. Therefore it is presumed  
10 that the suppression in blood glucose-increase is rather caused by retardation of the absorption arising from the slight inhibition of the absorption.

On the other hand, when a high dose (0.1 mg/kg) or a low dose (0.03 mg/kg) of this drug was administered to  
15 SD rat in concurrence with the sucrose loading, the inhibition of the elevation of blood glucose level was observed in both doses. The observation revealed the following estimated results: in the high dose, some sucrose reached intestinum crassum without absorption, while in  
20 the low dose, sucrose could not be detected in intestinum crassum and all sucrose was absorbed in intestinum tenue.<sup>9)</sup> That is, the inhibition of the elevation of blood glucose level due to this drug was caused by mainly inhibiting absorption in the high dose. In contrast, in the low dose,  
25 the inhibition is caused by delaying of absorption resulting from gradual digestion and absorption during transportation of sucrose which was moderately inhibited from absorption

in the upper part or middle part of intestinum tenue to the bottom part thereof. The administration of 0.2 mg for a dose for human probably corresponds to the low dose for SD rat.

5           The average value of the area under concentration-time curve of the elevation of blood glucose level after the administration of this drug reduced to about 40% relative to that after the administration of the placebo. The decrease is probably caused by that glucose concentration  
10 in peripheral blood did not increase as the result of acceleration of glycogenesis in the liver due to gradual glucose absorption<sup>9)</sup> or as the result of occasional use of the absorbed glucose in the liver, skeletal muscle and other organs.

15           The change of the blood insulin approximately corresponded to that of the blood glucose. Compared with after the administration of the placebo, apparent inhibition of elevation was observed after the administration of this drug. As the same as in the blood glucose, with respect  
20 to the area under concentration-time curve of the elevation of blood insulin level as the basis for the value before the loading, the value after the administration of this drug reduced to about 60% relative to the value after the administration of the placebo. This shows that the delay  
25 of glucose absorption reduces the needed quantity and secretion quantity of the insulin.

The digestive symptom was not recognized after the

administration of the placebo, specifically, in the circumstance that the taken sucrose was wholly absorbed and there was no sucrose reached intestinum crassum. On the other hand, after the administration of this drug and after the lactulose loading, at both of which the unabsorbed carbohydrates probably reached intestinum crassum and were decomposed by bacterial flora, 4 subjects out of 12 subjects (loose stool (2 subjects), diarrhea (1 subject) and bloating sensation (1 subject)) and 2 subjects out of 12 subjects (bellyache (1 subject) and borborygmus (1 subject)) showed the digestive symptom, respectively. Therefore, the digestive symptom is probably developed due to decomposition of unabsorbed carbohydrates by bacterial flora in intestinum crassum.

In one subject who developed diarrhea, the possibility that carbohydrates which reached intestinum crassum without absorption were discharged from the subject's body without decomposition by intestinal bacterial flora cannot be denied. Therefore, the results of 11 subjects excluding this subject were also summarized. The AUC(A-P) was  $98.6 \pm 70.8 \Delta\text{ppm}\cdot\text{hr}$ , the AUC(L-P) was  $260.0 \pm 136.4 \Delta\text{ppm}\cdot\text{hr}$ , and the amount of sucrose which this drug inhibited from being absorbed was estimated to be  $5.3 \pm 3.3 \text{ g}$  as the average value. This average value hardly differed from the estimated value in total 12 subjects ( $5.0 \pm 3.3 \text{ g}$ ).

In diabetes, there is not enough absolute or relative action of insulin, and glucose absorbed by the living body



cannot be utilized efficiently. Therefore, the blood glucose level increases. As a result, development and advance of various acute or chronic complications are induced. Accordingly, the suppression of postprandial rapid elevation of blood glucose level by the administration of this drug probably reduces the risks of development and advance of diabetes complication.

Further, since this drug can inhibit elevation of blood insulin level, the availability of this drug is expected to lead to interruption of development and advance of coronary artery disease or arteriosclerosis<sup>10)</sup>, in which excessive insulin secretion or hyperinsulinemia are seriously involved.

Moreover, the amount of sucrose which this drug inhibited from being absorbed when 100 g of sucrose was administered was only about 5.0 g, and sucrose was mostly absorbed. In 0.2 mg of this drug for a dose, inhibition of carbohydrates absorption hardly occurred, and there was hardly any loss of the orally administered energy. Therefore, this drug will be expected as a therapeutically preferable agent for diabetes patients since this drug "absorbs every carbohydrate without elevation of blood glucose level".

#### CONCLUSION

This study was conducted for estimating the amount of unabsorbed carbohydrates in AO-128 administration on

healthy 12 subjects by using a measuring method for the concentration of the expired hydrogen gas and demonstrating the action mechanism of inhibition of the elevation of blood glucose level.

5           (1) By administrating 0.2 mg of this drug, the amount of unabsorbed sucrose was estimated to be about 5.0 g relative to loaded 100 g sucrose.

          (2) Compared with after the administration of the placebo, the apparent inhibition of the elevation of blood  
10 glucose and blood insulin levels was observed after the administration of this drug.

          (3) The action mechanism of inhibition of the elevation of blood glucose level caused by administration of 0.2 mg of this drug is based on delay of absorption  
15 resulting from gradual digestion and absorption during transportation of sucrose which was moderately inhibited from absorption in the upper or middle part of intestinum tenue to the bottom part thereof.

          From there results, high usefulness of this drug is  
20 expected for diabetes therapy.

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25 inhibitor AO-128 in rat for postprandial elevation of blood glucose level. Journal of Japanese Society of Nutrition and Food Science 45: No.1, 1992 (scheduled for publishing)

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- 5        3) Levitt MD: Production and excretion of hydrogen gas in man. N Engl J Med 281: 122-127, 1969
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insulin levels to the incidence of myocardial infarction and coronary heart disease mortality in a middle-aged population. Diabetologia 19: 205-210, 1980

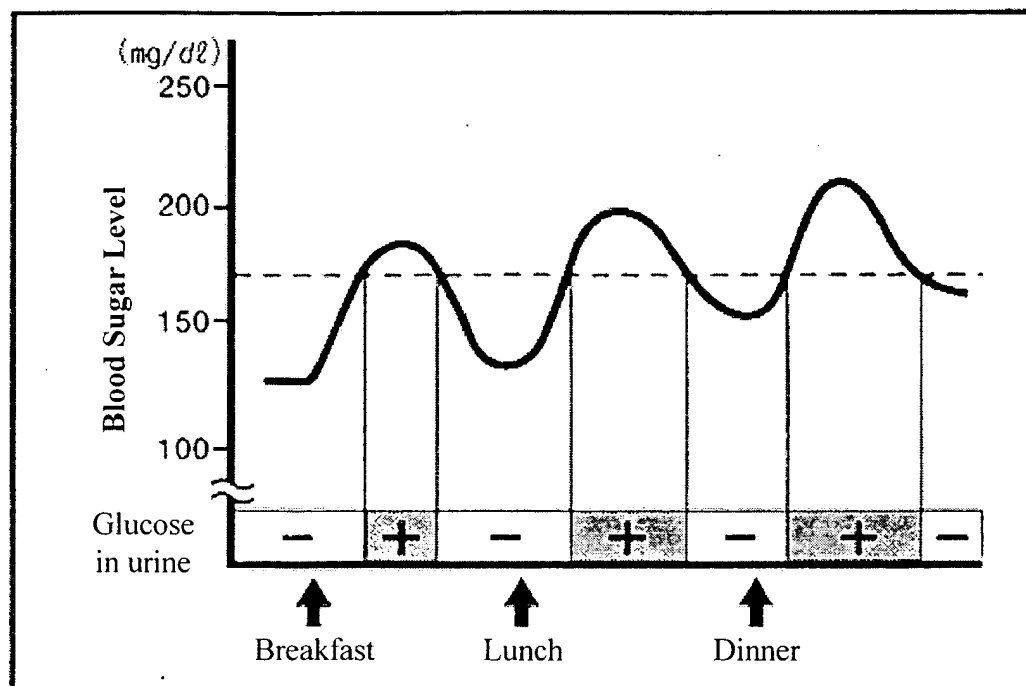
**Document E:** a copy of the web page "<http://www.kawasaki-dms.jp/general/rensai04/002.html>" opened to the public by a nonprofit organization "Kawasaki Diabetes Mellitus Square" obtained on April 21, 2009.

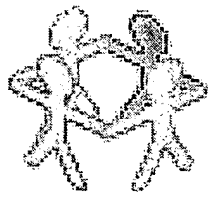
The paragraph bridging printed pages 2-3:

What is the case showing a positive value of sugar in urine?

Since glucose is an important energy source, kidneys have a system which does not excrete or waste glucose into urine. However, when too much sugar is transferred into the kidneys through the blood flow, the amount of sugar (glucose) is beyond the ability of the system and glucose leaks into urine. Such a blood-sugar level, which is a marginal blood-sugar level wherein the leakage of glucose into urine occurs at a level higher than the marginal level, is called "threshold of glucose evacuation into urine". Such thresholds are different among individuals but are about 170 to 200 mg/dl. Figure 1 shows an example of a change in a blood sugar level for a slight diabetic. The dotted line is drawn at 170 mg/dl and this value is the threshold for the diabetic. The threshold means that the blood level higher than the threshold results in positive for glucose in urine. The test result of glucose in urine for this diabetic is negative at preprandial and positive at postprandial. Preprandial blood sugar level is 70 to 100 mg/dl and postprandial blood sugar level is about 140 mg/dl for healthy adults. Thus, glucose in urine always shows negative value in spite of timing of the test for the healthy adults. Contrarily, a diabetic whose preprandial blood sugar is beyond the value about 170 mg/dl is always negative in glucose level in urine in spite of the timing of the test. Because the blood sugar level further increases after eating.

Figure 1. Example of a slight diabetic.





# 特定非営利活動法人 (NPO 法人) 川崎糖尿病スクエア

一般向け情報	
糖尿病の正しい知識を持ちましょう	NEW
生麦玉子の簡単料理で野菜たっぷり	NEW
川島由起子のこれならできる食事療法	NEW
糖尿病専門医のワンポイントアドバイス	NEW

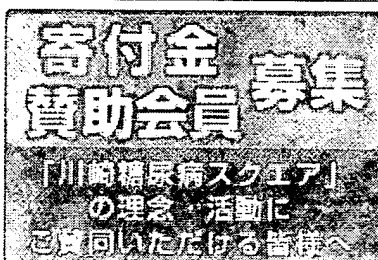
食物繊維は食後の血糖を改善します

受診される際のお願い

尿糖を測定してみませんか

血糖自己測定中の方へ

糖尿病人物往来	NEW
イベント紹介	NEW
臨床試験・治験のご案内	
会員施設紹介	



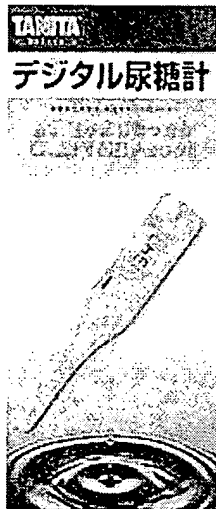
## 糖尿病専門医のワンポイントアドバイス

尿糖を測定してみませんか — 尿糖測定のポイントとコツ —

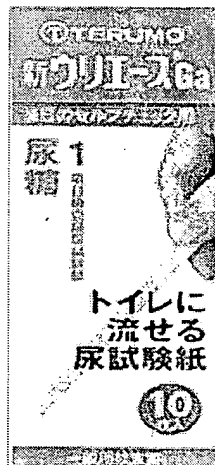
### 尿糖とは

尿糖とは文字通り尿中に含まれるブドウ糖のことです。人間は体外に排泄すべき老廃物を尿に溶かして捨てています。そのため尿には多くの老廃物が溶けていますが、タンパク質やブドウ糖など体に必要な物質はほとんど含まれません。尿を作っている臓器は言うまでもなく腎臓です。腎臓は24時間休まずに血液を濾過して老廃物を絶えず尿中に排泄していますが

同時にタンパク質やブドウ糖などの必要物は捨てないように選り分けています。すなわち腎臓は単に血液を濾過するだけでなく、体にとって不要物と必要物を取捨選択しています。健康人の尿中に含まれる尿糖量は厳密にはゼロではありませんが、その量はおおむね20 mg/dl未満(尿100 ml中に含まれるブドウ糖が20 mg未満)です。これは尿糖試験紙の感度以下であるため、測定しても陰性になります。尿糖検査は自宅で簡単に出来ます。写真は町の薬局で購入出来る尿糖試験紙ですが、1回ごとの使い捨て、測定後はトイレに流せるタイプで1回の費用は20～30円程度です。測定する時は尿糖試験紙を尿に浸し、所定時間後に試験紙の色の变化を色調表(色見本)と比較して判定します。また写真のように使い捨てではなく何回も測定出来る体温計に似た尿糖測定器具も発売されています。

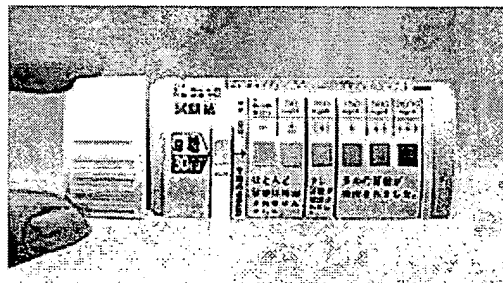


一尿糖測定器具の例



一尿糖試験紙の例

1 尿糖試験紙での結果の測定例



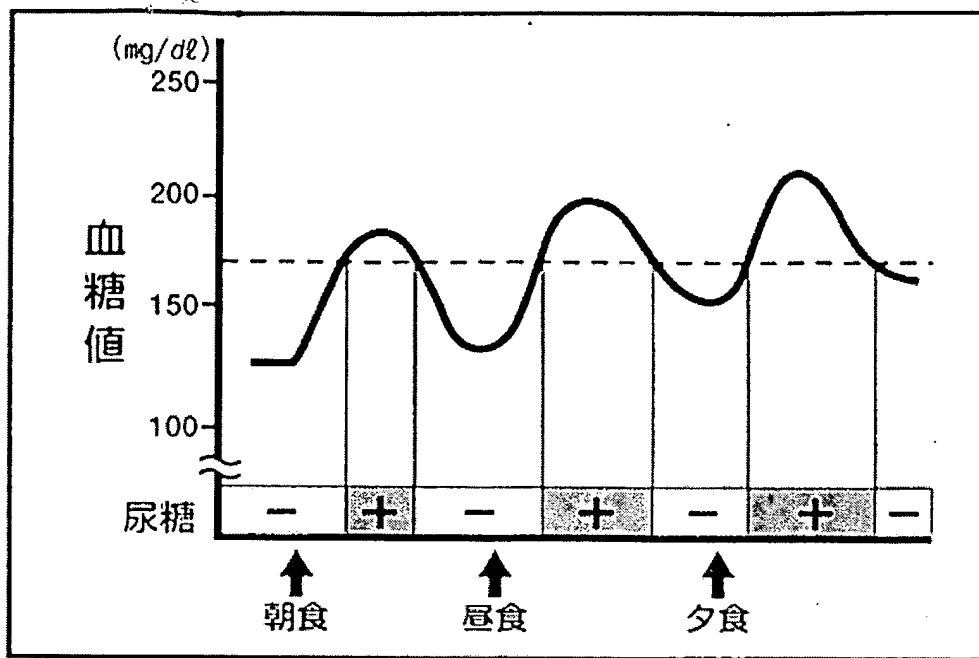
[ページトップへ↑](#)

#### 尿糖が陽性になる場合とは

ブドウ糖は大切なエネルギー源ですから、腎臓には尿中にブドウ糖を捨てない仕組みが備わっています。しかし、腎臓に流れてくる血液中の血糖が高すぎると、この仕組みの限界を超えてしまうため尿中にブドウ糖が漏れ出してしまいます。この時の血糖値、すなわちこれ以上に血糖が上がると尿にブドウ糖が漏れてしまう限界の血糖値を「尿糖排泄閾値(にようとうはいせついきち)」と呼びます。尿糖排泄閾値には個人差がありますが、おおむね170～200 mg/dl程度です。図1は軽い糖尿病患者さんの例です。点線が170 mg/dlの位置に引いてありますが、これがこの方の尿糖排泄閾値です。これ以上の血糖値であれば尿糖が陽性になることを意味します。この方は食前に検査すると陰性ですが、食後に検査すると陽性になります。健康な方は食前血糖が70～100 mg/dl、食後血糖でも140 mg/dl程度ですから、いつ検査しても尿糖は陰性です。逆に、食前血糖がすでに170 mg/dl程度を超えている糖尿病の患者さんでは、食後はさらに血糖が上がるため、いつ検査しても常に尿糖は陽性です。

図1. 軽い糖尿病患者さんの一例





一つ注意しないといけない点は、尿糖排泄閾値が120～150 mg/dl程度と異常に低い方がおられることです。これは遺伝的な原因で腎臓の尿糖排泄閾値が低くなっており、糖尿病でない状態でも食後の尿糖が陽性になります。残念ながらこのような方には尿糖検査は有用とはいえません。

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### 尿糖測定の実際

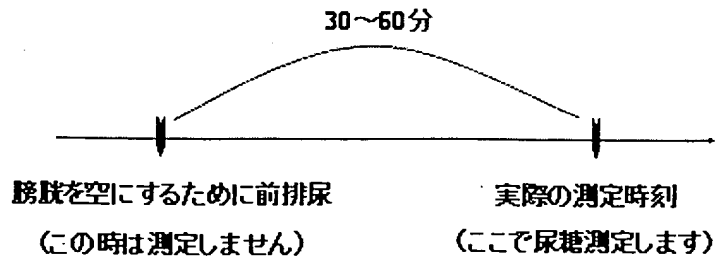
ほとんどの尿糖試験紙は尿中に含まれる尿糖の程度により、(-)から(±)、(+)、(++)、(+++)までの5段階の色調を呈します。血糖が尿糖排泄閾値を超えると尿糖陽性になりますが、血糖がさらに上昇するほど、より多くの尿糖が排泄されますから、尿糖が(++++)の場合と(+)の場合とでは、その時の血糖値も異なることを意味します。従って、一口に尿糖陽性といっても、その程度が少なくなってくれば血糖値が改善してきたと考えられますし、尿糖が陰性になれば血糖値はおおむね170～200 mg/dlを切ったと考えることができます。

[ページトップへ↑](#)

### 尿糖測定のポイントは前排尿です

尿糖の測り方のポイントを一言でいえば、図2のように測りたい30～60分前に一度排尿することです。但し、この時は測定しません。これは膀胱に溜まっていた尿を排泄して、一旦膀胱を空にするためです。この時から30～60分後に貯まった僅かな尿を排尿して測定します。なぜこのような手間なことをするのでしょうか。尿糖を測定する目的はあくまでその時の血糖の程度を大まかにつかむためです。血糖は刻々と変化していますが、膀胱に貯まった尿中の尿糖は前回の排尿から今回の排尿までの時間に産生された尿全体の尿糖を反映しています。従って、測りたい時間の血糖の程度を推測するには、出来るだけその時間帯に産生された尿だけで検査の方がより正確と考えられるからです。

図2. 尿糖測定のポイント



[ページトップへ↑](#)

#### 尿糖はいつ測ればよいか

図1のような境界型または軽い糖尿病の方では食前尿糖は陰性で、食後のみ陽性になることが多いですから、尿糖測定は食後2時間頃に行いましょう。尿糖の測定結果から血糖値が正確に分かるわけではありませんが、一定の時刻に尿糖を継続的に測定していると、自分自身の血糖変動をある程度推測することが出来ます。例えば、普段の食事なら食後2時間尿糖が(+)なのに、カロリーが多い食事を摂った時は(+++)であれば、普段以上に食後血糖が高いことが分かります。生活習慣を改善して体重も減少し、それまで食後2時間尿糖が(+)であったのが(―)になってくると、食後2時間血糖が少なくとも170～200 mg/dlのレベルを切ったのではないかと考えられます。このように、境界型や軽い糖尿病の方では食後尿糖の陰性化が最初の目標となり、そのために食後2時間前後の尿糖を測定しましょう。

逆に食前血糖が200 mg/dlを超えているような糖尿病の方では食前尿糖を主に測定し、先ず食前尿糖の陰性化を目指します。食前尿糖が陰性化すれば、その後は食後尿糖を測定します。血糖自己測定を行っている方は、食前と食後をおりまぜて血糖測定と尿糖測定を同時に行ってみましょう。継続的に両者の結果を見比べていく間に、自分自身の尿糖排泄閾値がどれくらいの値なのか見当がついてきますし、尿糖の程度により大まかな血糖を推測することも出来るようになります。

[ページトップへ↑](#)

#### 先生や医療スタッフの方とご相談を

血糖自己測定は痛みを伴いますが、尿糖測定は手軽で痛くありません。一般的な試験紙はトイレに流せるタイプが多いですから誰でも簡単に測定出来ます。そして測定した結果を有効に活用することが大切です。測定した結果と測定時刻、食事との時間関係をノートに記録しましょう。さらに、その日の体調や食事内容、薬剤内服やインスリン注射を行っている場合はその時刻などもノートに記入しておきます。血糖を同時測定した場合はそのデータも記録します。これらは血糖コントロールを良くするための貴重な情報源になります。先生やスタッフの方ともよくご相談の上で、尿糖測定を有効活用して頂ければ幸いです。

[ページトップへ↑](#)

Revised: December 2006 (11<sup>th</sup> version)

Standard Commodity Classification No. of Japan

873969

- Improving agent for postprandial hyperglycemia in diabetes mellitus -  
 <Japanese Pharmacopoeia, Voglibose tablets>

**BASEN<sup>®</sup> Tablets 0.2****BASEN<sup>®</sup> Tablets 0.3**

Designated drug, Prescription drug

Storage
Store at room temperature.

Expiration date
Do not use after the expiration date indicated on the package. (Use as soon as possible after unsealing, even before the expiration date.)

	Tablets 0.2	Tablets 0.3
Approval No.	(6AM)1120	(6AM)1121
Date of listing in the NHI reimbursement price	August 1994	August 1994
Date of initial marketing in Japan	September 1994	September 1994
Date of latest reexamination	September 2004	September 2004

Caution - Use only pursuant to the prescription of a physician etc.

**CONTRAINDICATIONS (BASEN<sup>®</sup> Tablets are contraindicated in the following patients.)**

- (1) Patients with severe ketosis, or in a state of diabetic coma or pre-coma [Since it becomes essential to quickly rectify hyperglycemia with administration of intravenous fluid or insulin, the use of BASEN<sup>®</sup> Tablets is not suitable.]
- (2) Patients with severe infections, before or after operation, or with serious trauma [It is desirable to control blood sugar with the injection of insulin. Therefore, administration of this drug is not appropriate.]
- (3) Patients with a history of hypersensitivity to any of the ingredients of this drug

**INDICATIONS**



Improvement of postprandial hyperglycemia in diabetes mellitus (However, BASEN<sup>®</sup> Tablets should be used only when sufficient effect has not been obtained in patients already undergoing dietary treatment and/or exercise therapy, or when sufficient effect has not been obtained in patients who have been using oral hypoglycemic drugs or insulin preparations, in addition to dietary treatment and/or exercise therapy.)

**DOSAGE AND ADMINISTRATION**

Usually, for adults, BASEN<sup>®</sup> Tablets are orally administered in a single dose of 0.2 mg as voglibose, three times a day, just before each meal. If the effect is not sufficient enough, the single dose may be increased up to 0.3 mg, under close observation of the course of disease.

**DESCRIPTION**

This drug is Voglibose tablets (Japanese Pharmacopoeia).

	BASEN <sup>®</sup> Tablets 0.2	BASEN <sup>®</sup> Tablets 0.3
Active ingredient per tablet	Voglibose 0.2 mg	Voglibose 0.3 mg
Dosage form	Plain-scored tablets	Plain tablets
Color of tablet	White to yellowish - white	
Identification Code	⊙ 351	⊙ 352
Appearance	Top Bottom Side 	Top Bottom Side 
Diameter (mm)	7.1	8.1
Thickness (mm)	2.6	3.1

Inactive ingredients:

Com Starch, Hydroxypropylcellulose, Magnesium Stearate, Lactose

**PRECAUTIONS****1. Careful Administration (BASEN<sup>®</sup> Tablets should be administered with care in the following patients.)**

- (1) Patients who are receiving other antidiabetic drugs [Hypoglycemia may occur.] (See 4. (1) Clinically significant adverse reactions.)
- (2) Patients with a history of laparotomy or ileus [Intestinal obstruction-like symptoms are liable to develop due to an increase in intestinal gas, etc.]
- (3) Patients with chronic intestinal disease accompanied by a disturbance in digestion and absorption [The actions of this drug may aggravate the pathologic condition.]
- (4) Patients with Roemheld's syndrome, severe hernia, or stenosis or ulceration of the large intestine, etc. [Symptoms may worsen due to an increase in intestinal gas, etc.]

- (5) Patients with serious hepatic dysfunction [Because of possible changes in metabolic condition, the status of blood sugar control may greatly vary. In patients with severe liver cirrhosis, hyperammonemia may worsen, followed by disturbance of consciousness.]
- (6) Patients with serious renal dysfunction [Because of possible changes in metabolic conditions, the status of blood sugar control may greatly vary.]
- (7) Elderly patients (See 5. Use in the Elderly.)

## 2. Important Precautions

- (1) The administration of BASEN® Tablets should be limited to the patients who have been definitely diagnosed as having diabetes mellitus. It should be noted that in addition to diabetes mellitus, there are such diseases as abnormal glucose tolerance and positive urinary sugar that represent diabetes-like symptoms (renal glucosuria, senile abnormal glucose tolerance, abnormal thyroid function, etc.).
- (2) For patients who are undergoing only the basic treatment for diabetes mellitus, namely, dietary treatment and/or exercise therapy, this drug should be given only when the two-hour postprandial blood sugar is 200 mg/dl or more.
- (3) For patients who are using oral hypoglycemic drugs or insulin preparations, in addition to dietary treatment and/or exercise therapy, a rough standard for administration of this drug is to give it when the fasting blood sugar is about 140 mg/dl or more.
- (4) During administration of BASEN® Tablets, the progress of disease should be closely observed with the monitoring of blood sugar at regular intervals, and careful attention should always be paid to the question of necessity for continuous administration of this drug. If its effect on postprandial blood sugar is not satisfactory even after the administration of this drug for 2 to 3 months (e.g. the reduction in the two-hour postprandial sugar level in venous plasma to 200 mg/dl or below can not be achieved), such consideration as the change to more possible appropriate treatment should be made. When sufficient control of the postprandial blood sugar has been attained (the two-hour postprandial sugar level reduced to 160 mg/dl or below in venous plasma), and is judged to be satisfactorily maintained only with dietary treatment and/or exercise therapy, or with additional use of oral hypoglycemic drugs or insulin preparations, the administration of BASEN® Tablets should be discontinued and the subsequent progress of disease be observed.
- (5) In administration of BASEN® Tablets, the patients should be given the sufficient explanation on hypoglycemic symptoms and as to how they will be coped with. (See 4. (1) Clinically significant adverse reactions.)

## 3. Drug Interactions

**Precautions for coadministration (BASEN® Tablets should be administered with care when coadministered with the following drugs.)**

Drugs	Signs, Symptoms, Treatment, Mechanisms, etc.
<b>Antidiabetic drugs</b> Derivatives of sulfonamide and sulfonylurea, biguanide derivatives, insulin preparations and improving agents for insulin resistance	It has been reported that hypoglycemia occurred in the concomitant use of BASEN® Tablets with insulin preparations or sulfonylurea derivatives. Therefore, when this drug is used in combination with any of the left-listed drugs, such careful caution as starting from a lower dose should be exercised, taking into account the possible development of hypoglycemia.
<b>For the concomitant use of antidiabetic drugs and the drugs which enhance or diminish the hypoglycemic action of antidiabetic drugs</b> ◊ Drugs enhancing the hypoglycemic action of antidiabetic drugs: β-blockers, salicylic acid preparations, monoamine oxidase inhibitors, fibrate derivatives for treatment of hyperlipemia, warfarin, etc. ◊ Drugs diminishing the hypoglycemic action of antidiabetic drugs: Epinephrine, adrenocortical hormone, thyroid hormone, etc.	When BASEN® Tablets are further administered concurrently, in addition to the concomitant use among any of the left-listed drugs, careful attention should be paid to the drug interactions listed in the package inserts of these antidiabetic drugs. Further cautious attention should also be paid to the influence that might be additionally caused by the delaying action of this drug on the absorption of carbohydrates.

## 4. Adverse Reactions

Adverse reactions, including abnormalities in laboratory data, were observed in 154 (16.0%) of 965 patients given the daily doses of 0.6 mg or 0.9 mg of BASEN® Tablets in the investigation performed up to the time of approval, and in 460 (10.3%) of 4,446 patients in the postmarketing investigation of the results of drug use (as of the end of re-examination).

Adverse reactions listed below have been found in the above-mentioned investigations, spontaneous reports, etc.

### (1) Clinically significant adverse reactions

- 1) When BASEN® Tablets are used in combination with other antidiabetic drugs, hypoglycemia may occur (0.1% - < 5%). Furthermore, hypoglycemia has been reported to occur (< 0.1%) even when other antidiabetic drug was not concomitantly used with this drug. This drug delays the digestion and absorption of disaccharides. Therefore, if any hypoglycemic symptom is observed, such appropriate measures as the administration of glucose instead of sucrose should be taken.
- 2) Abdominal swelling, increased flatus, etc., may occur (0.1% - < 5%), and intestinal obstruction-like symptom due to an increase in intestinal gas, etc., may occur (< 0.1%). Therefore, close observation should be made, and if any of such symptoms occurs, appropriate measures, such as discontinuation of BASEN® Tablets, should be taken.
- 3) Fulminant hepatitis, serious hepatic dysfunction with increased AST (GOT), ALT (GPT), etc., or

jaundice may occur (each < 0.1%). Therefore, close observation should be made, and if any abnormality is found, the administration should be discontinued and appropriate measures taken.

- 4) When BASEN® Tablets are administered to the patients with serious liver cirrhosis, hyperammonemia may worsen with the development of constipation, etc., followed by disturbance of consciousness (frequency unknown). Therefore, the condition of bowel movement, etc., should closely be observed, and if any abnormality is observed, such appropriate measures as immediate discontinuation of this drug should be taken.

#### (2) Other adverse reactions

	0.1% - < 5%	< 0.1%	frequency unknown
1) Gastrointestinal	Diarrhea, loose stools, borborygmus, abdominal pain, constipation, anorexia, nausea, vomiting or heartburn	Stomatitis, thirst, taste abnormality or pneumatosis cystoides intestinalis	
2) Hypersensitivity Note 1)		Rash, pruritus, or photosensitivity	
3) Hepatic	Increased AST(GOT), ALT(GPT), LDH, $\gamma$ -GTP or ALP		
4) Psychoneurologic		Headache, dizziness, light-headedness or sleepiness	
5) Hematologic	Anemia	Thrombocytopenia	Granulocytopenia
6) Others	Numbness, edema of face etc., blurred vision, hot flushes, malaise, weakness, hyperkalemia, increased serum amylase, decreased HDL cholesterol, diaphoresis or alopecia		

Note 1) In such a case, administration of BASEN® Tablets should be discontinued.

#### 5. Use in the Elderly

Since the elderly have a physiological hypofunction in general, the administration of BASEN® Tablets should be initiated at a lower dose (e.g. single dose of 0.1 mg). Furthermore, this drug should be carefully administered under close observation of the course of disease conditions, with careful attention to the blood sugar level and the onset of gastrointestinal symptoms.

#### 6. Use during Pregnancy, Delivery or Lactation

- (1) BASEN® Tablets should be administered to pregnant women or women having possibilities of being pregnant only if the expected therapeutic benefit is thought to outweigh any possible risk. [The safety of this drug in pregnant women has not been established.]

- (2) It is desirable to avoid the administration of this drug to nursing mothers. However, if the administration is indispensable, nursing should be discontinued. [Animal studies (rats) have revealed a suppressive action of this drug on body weight increase in newborns, presumably due to suppression of milk production resulting from inhibition of carbohydrate absorption in mother animals.<sup>1-2)</sup>]

#### 7. Pediatric Use

The safety of BASEN® Tablets in children has not been established (no clinical experience).

#### 8. Precautions concerning Use

When dispensing the drug:

The patient must be instructed to remove the tablets from the press-through package (PTP) before they are ingested. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, and this could result in serious complications such as mediastinitis.]

#### PHARMACOKINETICS

- (1) When BASEN® Tablets were repeatedly administered to healthy male adults (6 subjects) in a single dose of 0.2 mg, three times a day, for 7 consecutive days, no voglibose was detected in plasma or urine.<sup>3)</sup>  
(For reference) In administration of this drug to healthy male adults (10 subjects) in a single dose of 2 mg, no voglibose was detected in plasma or urine.
- (2) In a study in which a single dose of 1 mg/kg of [<sup>14</sup>C] voglibose was administered to rats, the transfer of voglibose to fetus and mother's milk was observed, and the rates of excretion into urine and feces were about 5% and 98%, respectively.<sup>4)</sup>

#### CLINICAL STUDIES<sup>5-20)</sup>

In various clinical studies, including double-blind comparative controlled clinical trials, in which BASEN® Tablets were administered in daily doses of 0.6 mg or 0.9 mg to patients with non-insulin-dependent diabetes mellitus or insulin-dependent diabetes mellitus, the improvement rates by the type of diabetes mellitus in 877 patients, who were included in the analysis of the final global improvement rating in blood sugar, were as shown in the table.

Type of diabetes mellitus	Number of patients	Improvement or better evaluation	Slight improvement or better evaluation
Non-insulin-dependent diabetes mellitus	812	371 (45.7)	613 (75.5)
Insulin-dependent diabetes mellitus	65	31 (47.7)	47 (72.3)
Total	877	402 (45.8)	660 (75.3)

Figures denote the number of patients, and figures in parentheses indicate the

cumulative %.

Improvement or better evaluation: "marked improvement" + "improvement"

Slight improvement or better evaluation: "marked improvement" + "improvement" + "Slight improvement"

The usefulness of BASEN® Tablets has been proved in double-blind controlled clinical trials in the above-cited patients with non-insulin-dependent diabetes mellitus.<sup>5-6)</sup> The usefulness of this drug, including improvement of postprandial hyperglycemia, has also been recognized not only in patients undergoing dietary treatment alone but also in patients using insulin preparations<sup>7-10)</sup> or oral hypoglycemic drugs.<sup>11-15)</sup> In addition, in long-term administration study (for an average of 7 months), the lasting efficacy of this drug has been confirmed, and stable control of blood sugar has been attained.<sup>16-20)</sup>

The results of the clinical pharmacological tests have revealed that the typical adverse reactions pertaining to BASEN® Tablets, such as increased flatulence, feeling of enlarged abdomen, diarrhea or loose stools, etc., are considered to be attributable to decomposition and fermentation of unabsorbed carbohydrate resulting from pharmacological actions of this drug.

## PHARMACOLOGY<sup>21-28)</sup>

Voglibose inhibits the hydrolase ( $\alpha$ -glucosidase) for disaccharides that catalyzes decomposition of disaccharides into monosaccharides in the intestine, thereby delaying the digestion and absorption of carbohydrate, resulting in improvement of postprandial hyperglycemia.

### 1. Mechanism of action<sup>21)</sup>

- (1) Voglibose exhibits the inhibitory actions on porcine small intestine-derived maltase and sucrase, which are about 20 and 30 times as strong as acarbose, respectively, while the inhibitory actions of voglibose on rat small intestine-derived maltase and sucrase are about 270 and 190 times as strong as those of acarbose, respectively (in vitro). On the other hand, the inhibitory actions of voglibose on porcine and rat pancreatic  $\alpha$ -amylase are about 1/3,000 of those of acarbose, and voglibose produces no inhibitory action on  $\beta$ -glucosidase (in vitro).
- (2) The mode of inhibitory action of voglibose on the disaccharide hydrolase for the complex of rat small intestine-derived sucrase and isomaltase is competitive antagonistic (in vitro).

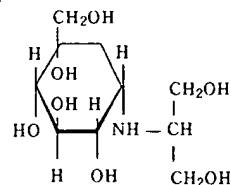
### 2. Suppressive action on increase in blood sugar

- (1) When administered orally to normal rats, voglibose suppresses the blood sugar increase resulting from the loading of starch, maltose and sucrose. However, it is ineffective in suppressing the blood sugar increase resulting from the loading of glucose, fructose and lactose (in vivo).<sup>21)</sup>
- (2) When healthy adults were loaded with sucrose and their expired hydrogen gas was measured, suppressive action of voglibose on increase in blood sugar at clinical doses was presumed to be attributable to slight inhibition of the absorption of carbohydrate based on its partial suppressing action on the decomposition of di-

saccharides, resulting in delayed absorption of carbohydrate.<sup>22)</sup>

## PHYSICO-CHEMISTRY

Structural formula:



Nonproprietary name:

Voglibose [JAN]

Chemical name:

3,4-Dideoxy-4-[2-hydroxy-1-(hydroxymethyl)-ethyl amino]-2-C-(hydroxymethyl)-D-*epi*-inositol

Molecular formula:

$C_{10}H_{21}NO_7$

Molecular weight:

267.28

Melting point:

163~168°C

Description:

Voglibose occurs as white crystals or crystalline powder. It is very soluble in water, freely soluble in acetic acid (100), slightly soluble in methanol, very slightly soluble in ethanol (99.5). It is soluble in 0.1mol/L hydrochloride solution.

## PACKAGING

Tablets 0.2:

100 tablets (10 tablets  $\times$  10), 500 tablets (loose, 10 tablets  $\times$  50), 1,000 tablets (10 tablets  $\times$  100), 2,100 tablets (21 tablets  $\times$  100)

Tablets 0.3:

100 tablets (10 tablets  $\times$  10), 500 tablets (loose, 10 tablets  $\times$  50), 1,000 tablets (10 tablets  $\times$  100), 2,100 tablets (21 tablets  $\times$  100)

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**REQUEST FOR LITERATURE SHOULD BE MADE TO:**

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